TYPHUS FEVER.

BY

EDWARD C. HORT, F.R.C.P. EDIN.,

PHYSICIAN TO ADDINGTON PARK FEVER HOSPITAL; DIRECTOR OF THE
CONSTANCE TROTTER RESEARCHES.*Synonyms.*

EPIDEMIC fever, spotted fever, putrid fever, gaol fever, camp fever, fourteen-day fever, malignant fever, petechial fever.

French, Typhus exanthématique; *German*, Flecktyphus; *Italian*, Tifo esantematico; *Dutch*, Vlekkoorts; *Spanish*, Tabardillo.

HISTORICAL SKETCH.

From the days of Hippocrates down to 1759 the word "typhus" (*tuphos* = fog) was used to denote a stuporous mental condition, without particular reference to individual diseases, or groups of diseases. In 1759 Boissier de Sauvages applied the term to a group of diseases in which mental hebetude might be observed. This group included what we now know as typhus.

In 1810 typhus fever was defined as a separate disease from typhoid by von Hildebrand, this term being applied to enteric fever by Louis in 1829. Von Hildebrand's claim for enteric as a distinct entity was confirmed by Bretonneau in 1813, by Gerhard and Pennock in 1837, and by Jenner about 1850.

Typhus fever is possibly the same disease as the plague of Athens described by Thucydides. It certainly was known in Italy, France, and Hungary in the sixteenth century, as described by Frascatorius of Verona.

In epidemic form the disease has repeatedly accompanied and followed war, attacking the camp, the beleaguered city, and the retreating host with impartial malignity. This was particularly the case between the siege of Reading in 1643 and the Crimean campaign.

Its ravages in Serbia in the spring of 1915 defy description. On March 31st no fewer than 3,000 fresh cases were reported from Skoplje alone.

In times of peace epidemics, till towards the end of the last century, were frequent in countries in which the disease held an endemic footing. Since the advent of the modern medical officer of health epidemics of alarming proportions have become rare in all countries in which he has had a free hand. In no disease has modern sanitation in its early days won greater triumphs than in typhus, unassisted by bacteriological research or by a knowledge of the bionomics of vermin. "The history of typhus," said Hirsch in 1893, "is written in those dark pages of the world's history which tell of the grievous visitations of mankind by war, famine, and misery of every kind." The knowledge we now possess of the etiology of the disease makes clear the inner meaning of Hirsch's inimitable summary.

GEOGRAPHICAL DISTRIBUTION.

In epidemic form, typhus, speaking generally, is a disease of cold or temperate climates. The tendency to overcrowding, stimulated by inclement meteorological conditions, has long been recognized as a dominant factor in the endemicity of typhus. Its geographical distribution is thus explained, certain parts of Russia, British North America, the United States, and Ireland affording familiar illustrations. Into tropical and subtropical areas the disease is sometimes introduced, and endemic centres thus established give rise to intermittent epidemic invasions.

METHOD OF SPREAD OF THE DISEASE.

It has long been known that clothes play an important part in endemic centres and in epidemic outbreaks. The Spanish equivalent for the disease—*tabardillo*, denoting a peasant's cloak—speaks eloquently of the connexion between clothes and typhus, and of the Spanish power of observation. It has also long been suspected that the connecting link between clothes and typhus was the presence of vermin, and as long ago as 1876 Murchison declared that to prevent infection with typhus it was essential that the body should be protected from lice. That Murchison's clinical observations were sound was amply confirmed by the experiments of Ch. Nicole, C. Comte, and E. Conseil in 1909, and by Anderson and Goldberger in 1910, who at the same time exculpated the bed bug and the flea. As an illustration of the connexion between endemic centres of the disease and epidemic outbreaks through the medium of vermin-infected clothes

may be cited an experience during a study of the bacteriology of the disease in an epidemic in Ireland in 1914. It was found that between Glasgow, a well-known endemic centre, and a certain part of the west of Ireland, where the epidemic occurred, there is an extensive trade in old clothes, which can be bought by the peasants for a few pence; inspection of the clothes in an infected house showed large numbers of lice.

Lice, however, are probably not the only carriers of the infective agent of the disease, as was shown in 1914 by Hort and Ingram, who were able to reproduce in bonnet monkeys a disease which appeared to be a modified form of typhus by the injection of first cultures on human blood-agar of a minute coccobacillus recovered from fresh typhus urine. This organism, which is of a pleomorphic type, is small enough, as it occurs in the body fluids, to pass tested Berkefeld filters, and can often be seen in large numbers in the centrifuged deposits of fresh human typhus urine. These observations suggest that the urine of typhus patients may be highly infective, and independent confirmation of the infectivity of excreta from typhus cases was recently obtained by C. E. Burns. This observer showed that in the island of Eriskey, in the Outer Hebrides, an outbreak of typhus could be traced with considerable confidence to a recent disturbance of a midden which had been in use by a family all of whom had died of typhus several years previously. The possibility of the disease being conveyed by the urine of convalescing and of chronic typhus carriers has not yet been investigated, but there is little doubt that during an attack of typhus a patient is an acute urinary carrier, and that the latter shares with the louse the stigma of being able to impart the causal organism of the disease.

PREVENTION OF SPREAD OF TYPHUS.

The methods to be adopted in arresting the spread of typhus in a quiescent community are easier of execution than in the case of a community disturbed by war.

In times of peace the danger of infection by lice should not be considered as adequately provided against by the employment of the various parasiticides which are widely recommended for the destruction of the louse in clothing or on the skin. The reason for this is that the favourite habitat for the louse in body clothing is under the lining and in the pleats, where he is relatively protected, and a false sense of security is therefore created by reliance on ointments, powders, vapours, and the like. Whenever possible, all personal clothes, bed-linen, mattresses, and so forth, from known cases of the disease should be thoroughly heated, or, if practicable, burnt, and careful search for lice on the skin and in the hair should be made, and these precautions should be observed before admission to hospital. After admission to hospital careful watch should still be kept for lice, in order to be certain that none have escaped detection, and for each patient arrangements should be made for the direct discharge of urine into vessels containing a 1 in 20 solution of carbolic, or other efficient disinfectant.

Incontinence of urine in typhus is not uncommon in severe cases, and special arrangements to prevent infection from soiled linen must therefore be made. In quiescent populations, provided that the points referred to are rigorously insisted upon, there is no danger in attending typhus patients, as is shown by the remarkable immunity enjoyed by doctors and nurses in modern hospitals.

In times of war the difficulties of controlling the spread of the disease are greatly enhanced, and the reason, therefore, for wholesale destruction of infected clothing, whenever practicable, and of disinfection of urine, becomes correspondingly increased. In dealing with grave epidemics, such as are now ravaging Serbia, the first essential for successful control is an unlimited stock of hospital tents, which should be frequently moved, unlined clothing which will stand dry heat, and large galvanized tanks containing carbolic solution for the reception of infected urine.

CLINICAL COURSE OF THE DISEASE IN UNCOMPLICATED CASES.

The incubation period lasts about fourteen days. In some cases it may be as short as one day or two, in others as long as twenty days. This variation is, perhaps, partly due to the particular stage in the life-history of the causal

organism, relative to its derivation from a pre-existing case of the disease, at which it was ingested by the lice responsible for infection of the particular case. The termination of the incubation period is followed by a short prodromal space, characterized by indefinite malaise. This leads up to rigors, fever, and pain in the back and lower limbs. The face may be early congested and even cyanosed.

On or about the fourth day a macular rash makes its appearance. It resembles that of measles, but is without the distinctive mouse smell of that disease. When the rash is fully developed there is often a characteristic odour from the skin, resembling that of a wet umbrella which is beginning to dry. The rash tends to appear first on the wrists and axillary folds. It then becomes abdominal, and subsequently invades the rest of the body, often missing, however, the face and neck.

Presently this measly rash is obscured by a subcuticular eruption of a peculiar mottled nature. The appearance now defies accurate description, but when once seen and learnt is almost pathognomonic. Soon after full development of the subcuticular rash profound toxæmia sets in, in severe cases, essentially characterized by heavy stupor, which may be disturbed by violent delirium or quiet muttering. In milder cases, as in children and the aged, there is no stupor, and there may be no signs of obvious illness. The spleen is not necessarily palpable, even in grave cases. After about fourteen days the continued fever of high range vanishes by crisis in uncomplicated cases, sometimes preceded by a fall between the eighth and tenth days. This, when it occurs, is characteristic of typhus, and is often to be seen in bonnet monkeys that have been injected with fresh typhus blood.

DIAGNOSIS.

A. Differential.

From enteric fever typhus can be early diagnosed by the presence of the *B. typhosus* in the blood and urine. It used to be considered that a negative Widal reaction gave a useful method of diagnosis of typhus from typhoid. We now know that the serum of typhus patients may give a reaction with emulsions of the *B. typhosus*, even in dilutions of high titre (W. J. Wilson). In cases in which early diagnosis between typhus and enteric is difficult or impossible the study of the temperature chart during the third week will often prevent error, provided that the case is uncomplicated.

From measles the disease can usually be recognized by the character of the subcuticular rash, the smell of the skin and the absence of Koplik's spots.

From uræmia cases of typhus with stupor can be distinguished by the presence of fever and the peculiar nature of the rash. From small-pox, with which in some epidemics there has been considerable difficulty in diagnosis, the absence of rash from the face is a useful guide.

B. Pathognomonic.

The most important points on which, when taken together, a positive diagnosis of typhus can be based, are:

1. The characteristic rash.
2. The smell of the skin.
3. A history of previous cases of the disease in the same house, especially if associated with lice.
4. The stuporous condition of severe cases presenting the rash.
5. The precritical fall of temperature.
6. The enormous relative and absolute increase in the large mononuclear cells in the blood.
7. The presence in blood films of the large diplobacillary and diplococcal organisms described by numerous observers.
8. Their presence also in fresh urine.
9. The presence in the centrifuged deposits of fresh urine of the minute Gram-positive, Gram-negative, pleomorphic organism described by Hort and Ingram.
10. The isolation and cultivation of the same organism from the blood and cerebro spinal fluid.
11. The results of injection of cultures of these organisms, or of fresh typhus blood, into bonnet monkeys.

Morbid Anatomy.

Owing to the relative shortness of the disease in fatal cases as compared with enteric wasting of the cadaver due to typhus is seldom extreme. Tissue autolysis is rapid, and rigor mortis is fugitive. Haemolysis is particularly rapid, and the vascular endothelium is often stained with haemoglobin. Subcutaneous petechiae persist after death. The cardiac muscle shows cloudy swelling and granular degeneration, and the spleen often tends to diffuence on opening of the capsule. Apart from these and other similar changes common to all acute infections characterized by profound toxæmia, there are no *post-mortem* changes known to us on which a diagnosis of typhus unsupported during life can reasonably be made.

Complications.

Pulmonary stasis is often met with, and lobar and lobular pneumonia are not infrequent. Jaundice is rare. Convulsions, not necessarily fatal, were observed in 132 cases in the London Fever Hospital between the years 1862 and 1869. Meningitis is a rare complication, which is somewhat surprising in view of the liability to infection of the cerebro-spinal fluid and the early onset of typhus coma in severe cases. Paresis of sphincters is not uncommon. Incontinence and retention of urine may both be present. Taken as a whole, the complications of typhus, except in fatal cases, are few and relatively unimportant.

BACTERIOLOGY.

The earliest observer to show experimentally that typhus is due to an infective agent, and that this may be present in the circulating blood, was Moczutkowsky. In 1875 he inoculated himself with blood taken from a typhus patient in the tenth day of fever, and after a latent period of eighteen days he became ill. He then rapidly developed a severe attack of typhus, which nearly cost him his life. This experiment was repeated in 1908 by Otero, and also by Yersin and Vassal, who stated that they had been able to produce the disease in two natives by the same method of experiment. Moczutkowsky's classical experiment was repeated, and its results were confirmed by Anderson and Goldberger and by Nicolle, Conseil, and Comte, and by others, by injection of monkeys with human typhus blood; these observers also found that the louse is an important, if not the most important, factor in the spread of the disease, thus confirming Murchison's observations from the clinical standpoint.

It was also shown by these observers that the infective agent is small enough to pass through coarse Berkefeld filters, though previous to 1914 it had not been seen or cultivated. Before dealing with recent work on the subject, it is necessary briefly to survey the bacteriological work carried out between 1883 and 1914 in the hope of discovering the causal organism of the disease.

In 1883 Mott and Blore reported the presence of dividing cocci in fresh typhus blood from 12 cases. In 1891 Ilkava of Prague obtained from the blood a streptobacillus in 20 out of 33 fatal cases. The organisms were cultivated on agar, in serum, and in bouillon. In 1893 Curtis and Albemarle obtained cultures of "diplococci" from the spleen in 3 fatal cases of the disease. In 1894 Dubieff and Bruhl described a "*Diplococcus exanthematicus*" which they obtained from the blood of 9 typhus patients. In 1906 Staniwechevskaja in 6 cases obtained cultures of similar organisms in blood bouillon, and in 1 case a "diplobacillus." In the same year Galesesco and Slatinéano in 4 cases reported cultivation from the blood of a Gram-positive "diplococcus," and in 6 cases a Gram-negative bacillus. The latter was also grown from the cerebro-spinal fluid in 8 cases, and in 4 cases a "diplococcus" was grown, and in the heart blood of 4 fatal cases Gram-positive "diplobacilli" were found. The Gram-negative bacillus produced acid but no gas from lactose; it coagulated milk, formed indol, and did not liquefy gelatine. It was non-motile, and it reddened the Drigalski medium. In 1908 M. Rabinowitsch described a "*Diplobacillus exanthematicus*" which he obtained from typhus blood. He said that in fresh cultures the organism was Gram-positive, and in old cultures Gram-negative. His optimum medium was glycerine ascitic broth.

In 1910 Wilson of Belfast reported that he had been able to cultivate in broth "diplococcal" organisms from the blood in 15 out of 33 cases of typhus, which he believed

to be identical with those cultivated by Staniwechevskaja. The organisms were Gram-positive, and gave a greyish film on agar and in gelatine, with a bluish tint by transmitted light. Subculture on agar from broth gave a growth which was quite unlike that of a *Staphylococcus aureus* or *albus*, and resembled that of *B. typhosus*. Gelatine began to liquefy in half the cases about the tenth day; in the remaining cases there was no liquefaction. The organisms fermented glycerine, galactose, maltose, laevulose, saccharose, mannite, dextrin, and lactose, but did not ferment sorbite, rhamnose, xylose, raffinose, arabinose, adonite, dulcitol, salicin, amygdalin, or inulin. They clotted litmus milk. Wilson also reported in one case the growth of an ovoid Gram-positive "diplobacillus," which behaved like the "diplococcal" organisms in every respect but that of fermenting glycerine and mannite. The agglutination of Wilson's organisms with typhus serum was in 13 cases five to twenty times that with normal serum. In 1913 Müller cultivated from the blood of 5 typhus patients "diplobacilli" and "diplococci," which he believes to be identical with the organisms described by M. Rabinowitsch in 1908 and by Fuerth and by Predjitschensky in 1893. The organisms were non-motile and appeared to be pleomorphic on subculture, cocco-bacillary forms being often seen. This appears to be the first record in the literature of the presence in typhus blood of pleomorphic organisms, with the exception of the large pleomorphic bacteria described by Fuerth and by Predjitschensky. In 1914 Gram-positive pleomorphic organisms were also recovered from typhus blood by Plötz, varying between 1 and 2 microns in length. There are in addition various other organisms, bacterial and quasi-protozoal, described by Gotschlich, Lewaschew, Thoinot and Calmette, and many others, and there is also a long list of observers who have failed to find in or cultivate from typhus blood organisms of any sort or description.

Perhaps the most striking fact brought out by a study of the literature is the large number of observers who have cultivated from the blood organisms of a diplococcal or diplobacillary nature.

Some of the observers quoted insist that the organism they describe is the *causa causans* of the disease. This is notably the case with the bacillus of Fuerth, restudied by Rabinowitsch, and again by Plötz. Analysis, however, of the evidence submitted is far from convincing, and the moderate view put forward by Wilson that both the *Diplococcus exanthematicus* and the diplobacillus are secondary organisms is one that appears to find more general acceptance. Moreover, as was shown by Hort and Ingram, the injection into monkeys of these large cocco-bacillary forms cultivated in citrated typhus blood consistently failed to produce a fever reaction. And there can be little doubt that, whether secondary invaders or not, they are not the primary cause of the disease. As a result of extensive observations in four different outbreaks of typhus in Ireland in 1914, Hort and Ingram found it difficult to believe that a theory of secondary invasion explains the frequency with which the organisms of Rabinowitsch, of Müller, of Fuerth, and of Plötz, organisms which appear to be identical, can be cultivated from typhus blood. They suggested therefore, as an alternative theory, that these organisms merely represent harmless phases in the life-history of organisms previously undescribed. This theory was based on the fact that they were able to demonstrate in, and cultivate from, fresh typhus blood, urine, and cerebro-spinal fluid a minute filter-passing organism which was proved to be infective to monkeys, from which the organism could be again recovered. This infective organism, both in film preparations of the fresh urine and cerebro-spinal fluid as well as in primary cultures in human blood, showed the same tendency to pleomorphism as the larger non infective forms. And there was some evidence that smaller forms still are present in the blood, urine, and cerebro-spinal fluid, but outside the range of vision, and that these smaller forms do not persist as such in artificial cultures. These results require repetition and confirmation by other observers, but there is little doubt but that a good case has been established for thorough investigation of the etiological claims of the organism in question.

PROGNOSIS.

Attacks of the disease vary greatly in their severity in different epidemics. In Brill's disease, believed to be a

modified form of typhus, the death-rate is usually low. In severe epidemics the dominant factor as regards a fatal issue in previously healthy subjects is age. The very young and the very old frequently escape with a light attack, even in severe epidemics. Robust adults between the age of 30 and 70 are said by those who see most of the disease to suffer severely, and to give the largest number of fatalities. In individuals exhausted by privation, exposure, fatigue, or disease, as in epidemics of war, the outlook is grave. Cases with early delirium, or stupor without delirium, do badly, as a rule. Sir John Moore gives the following prognostic data as unfavourable: A presentiment of death; soft, rapid, and compressible pulse in adults; feeble first sound; hurried respiration, not accounted for by pulmonary lesions; insomnia and delirium, complete coma-vigil and pin-hole pupils, extreme prostration, convulsions, muscular tremors and hiccough, early paresis of sphincters, tympanites, cyanosis, abundant and dark rash, persistent high fever, early profuse sweating, haemorrhagic manifestations.

In no grave disease is recovery so rapid or so complete as it may be after an attack of typhus.

TREATMENT.

The general treatment of typhus is that of any acute infective disease, and should be carried out whenever possible on open-air lines, due regard being paid to the avoidance of exposure.

Owing to the fact that previous to 1914 no satisfactory evidence was available as to the nature of the causative agent of the disease, specific treatment by vaccines or by antisera has not been possible for typhus. It is, however, not unreasonable to hope that confirmation of the etiological relationship to typhus of the organism described by Hort and Ingram will lead to the establishment of efficient protective, and possibly curative, methods of specific treatment.

[By permission of the Editor translations of this paper into French, Russian, and Serbian are being sent by the British Red Cross Society to Serbia and Russia.]

EPIDEMIC CEREBRO-SPINAL FEVER.

A NOTE ON PLEOMORPHISM OF THE RESPONSIBLE MICRO-ORGANISM.

BY FLEET-SURGEON E. A. SHAW, R.N., M.D. CANTAB.

IN connexion with the hypothesis as to the above put forward by Drs. Hort, Lakin, and Benians in the BRITISH MEDICAL JOURNAL for March 27th, I would like to contribute a few bacteriological notes on a case from a small epidemic I have been recently investigating, which appears both to support and to be explained by their hypothesis.

M. H., a youth of 18, became sick on March 14th with what appeared to be "rubella," but after twenty-four hours in an observation ward, had become so clinically pronounced a case of cerebro-spinal fever as to cause his prompt removal to the ward set apart for this disease.

On March 16th a throat swab was plated on nasagar, and cerebro-spinal fluid was drawn off aseptically, from which ascitic broth, nasagar slopes, and Petri dishes were inoculated. This fluid was decidedly turbid, and microscopically showed marked leucocytosis, but no micro-organisms of any sort.

On March 18th, after forty-eight hours' incubation at 37°, all the slopes, Petri dishes, and broth were sterile; there had been no growth at all. Lumbar puncture was repeated, turbid cerebro-spinal fluid was obtained under pressure. The case was now clinically as complete a case of cerebro-spinal fever as could be imagined; every sign and symptom was present, the only thing lacking was the bacteriological confirmation of the diagnosis. The same inoculation of slopes, etc., was repeated. Microscopically, this fresh specimen of cerebro-spinal fluid showed again marked leucocytosis, but again absolutely no micro-organisms.

On March 20th there was again no growth; everything was sterile. Lumbar puncture was repeated, and again decidedly turbid cerebro-spinal fluid was obtained. Nasagar slopes and plates were inoculated, and this time 1 c.cm. of cerebro-spinal fluid was added to each of two 10 c.cm. ascitic 2 per cent. glucose litmus broth tubes. Yet again, microscopically, leucocytosis was seen, but no micro-organisms.

On March 21st there was again no growth, and everything was returned to incubator: 8 c.cm. of blood were taken aseptically from the median cephalic vein, added to 50 c.cm. of ascitic broth, and incubated. I did not expect much from this, for the blood of previous cases had very rarely yielded the meningococcus of Weichselbaum.

On March 22nd there was no growth on the slopes or plates of March 20th; the ascitic glucose litmus broth contained a few